nerve cells in the cortex, of the lamina ganglionaris of the cornu ammonis, and in the amygdaloid nucleus. There is also an ischæmic softening in the stratum moleculare of the cornu ammonis. Vascular dilatation and hyaline thrombosis are again a prominent feature. When the distribution of the lesions in both series of experiments is examined it is clear that they lie in those parts of the brain and spinal cord which derive their blood supply from the vessels of the pia-arachnoid. The implication of the cornu ammonis and the amygdaloid nucleus does not, as might appear at first sight, contradict this statement; for the lamina involuta of the former is penetrated by folia of the pia-arachnoid, while the amygdaloid nucleus is continuous with the grey matter of the temporal lobe. The affected areas therefore possess this point in common that they depend upon the pial vascular system for their nutrition; and it is this special anatomical distribution, to the total exclusion of the central areas, which inclines one to the view that a general intoxication is by no means a satisfactory explanation of the genesis of the lesions. A considerable weight of evidence can be advanced in favour of the view that the sympathetic nervous mechanism may be an important factor in determining at which points a toxin circulating in the blood shall exercise its primary action upon the central nervous system. Our authority for making this statement is derived from the study of certain non-systemic lesions in the cord, and from the anatomy, physiology, and embryology of the so-called autonomic system. Non-systemic lesions occurring in the spinal cord are characterized by atrophy of the myelin sheath and sclerosis. They appear to be dependent on some toxic condition of the blood-stream, which attacks the myelin sheath in certain definite areas by some obscure mechanism. We have studied such lesions in cases of visceral cancer and in Addison's disease; and on account of certain features which they possess in common with the subacute combined sclerosis of the cord, associated frequently with severe anæmia, we propose to include this group in the description.

If the spinal cord is examined in cases of visceral cancer a non-systemic lesion will be found which varies in degree from case to case. As an illustration let us examine in some detail the cord from a case of carcinoma of the pyloric end of the stomach. This case showed a more extensive lesion than is usually found, but in its general features and localization it was typical. The cord lesions in visceral cancer affect the posterior and lateral columns; the fine fibres of the grey matter are rarely implicated and only in advanced cases; and the morbid

lesion consists in a slow atrophy and absorption of the myelin sheath accompanied by proliferation of the neuroglia. In the posterior columns the atrophic process varies in intensity in the cervical, dorsal, and lumbo-sacral regions. It is most marked, at all levels, round the postero-median septum and its area of maximum intensity changes frequently. Tracing it from above downward we find that from C1 to C3 it occupies a small area on either side of the posterior third of the septum. From C4 to C8, where the lesion is more pronounced than at any other level, it passes forward to occupy a more anterior position, until in C8 and in the upper six dorsal segments the areas immediately adjacent to the anterior third of the septum are most affected. From the level of D6 the area of atrophy progressively diminishes in size from above downwards and is shaped like an inverted V whose apex is directed towards the commissure and whose legs gradually diverge, on either side of the postero-median septum, towards the cord margin. The lesion at this level is of more recent date than that at a higher level. In shape it resembles closely the acute lesion found in the rabbit's cord after infection of the abdominal cavity. At the level of L1 there is some little degree of myelin atrophy confined to the fibres immediately surrounding the septal vessel and its branches, and from L3 downwards there is practically no change whatsoever.

The atrophic process accompanied by neuroglial proliferation begins round the postero-median septum, and progresses from within outwards. The lesion attains its maximum development between the fourth and eighth cervical segments, and in early cases we have observed that these and the highest dorsal segments are alone affected.

The lesion in the lateral columns is similar in nature to that of the sensory fibres but of less intensity. From C1 to C3 it is situated at the cord periphery and implicates both anterior and posterior cerebellar tracts. Below this level it occupies a more central position amongst the crossed pyramidal fibres and the lateral basis bundles. Similarly to the lesion in the posterior columns it diminishes in degree from above downwards and disappears almost entirely in the upper lumbar segments.

In Addison's disease the lesion in the spinal cord bears a remarkable resemblance to that in visceral cancer. It occupies the same position in the posterior columns. The morbid changes are more advanced in the cervical region and diminish from above downwards. They are of a more acute nature, however, and include more of the central portion of the posterior columns; while the histological picture presents certain

differences indicative of a more profound morbid disturbance. Weigert's method demonstrates that the medullated sheaths in the affected areas are totally destroyed; and in sections stained by Marchi's osmic acid method one finds the adventitial lymph spaces of the vessels in the degenerate area filled with the products of altered myelin stained jet black. Evidently, in this case, absorption of the altered myelin has not kept pace with its destruction, and injury to the axis-cylinder has in all probability been a contributory factor to rapid disintegration. There is evidence in other areas of the cord of implication of the axis-cylinder. For example, there are scattered patches of sclerosis in the anterior and lateral regions of the dorsal cord, and one of these has interrupted many fibres of the right crossed pyramidal tract, causing a descending degeneration.

In the lateral portion of the cord there is some degeneration situated at the periphery and extending from the cervical to the lumbar region. This is different from what is found in the lateral area of the cord in cancer cases, but agrees with the results of those experiments in which the medullated fibres round the cord periphery showed primary degeneration. The fine fibres in the grey matter of the upper dorsal and the cervical regions are atrophied to some extent; in the lower dorsal and lumbar segments they are practically intact.

There is another condition in which the spinal cord shows a degeneration similar in character and distribution to the above, though of a more severe nature. Subacute combined sclerosis gives rise to a definite clinical picture, and is frequently associated with severe anæmia. The lesion is more intense than in cases of cancer and Addison's disease, and on that account tends to obscure the pathogenesis, but an analysis of the morbid features shows that apart from intensity the same morbid process is at work.

The portion of the cord most affected is the mid-dorsal, where there is marked destruction of the white fibres round the entire periphery, leaving the grey matter and the fibres in its immediate environment perfectly normal. The exogenous and endogenous fibres of the posterior columns are affected equally. Above the mid-dorsal region the lesion becomes more limited, that is to say, it is confined to the central portions of the posterior columns, to the two cerebellar tracts, and to the crossed pyramidal tracts. In the cervical region there are also scattered areas of degeneration, a favourite site for them being the direct pyramidal tract and the neighbouring bundles. The destructive lesion is found as high as the upper portion of the medulla; the upper

limit of the pons, the internal capsule, and the cerebral cortex are perfectly normal. Below the mid-dorsal region the diffuse destructive lesion steadily diminishes in intensity, and in the lumbar region it is practically limited to the crossed pyramidal tract and to the posterior columns. Russell, Batten, and Collier [10] point out that we are obviously dealing here with a focal destructive lesion and system lesions dependent upon implication of ascending and descending tracts. The morbid process in its early stages is best seen at the margin of a degenerative patch. The myelin sheath first shows swelling, while the axis-cylinder remains normal. Later on, the sheath undergoes degeneration, and is absorbed, the axis-cylinder disappears, and sclerosis supervenes, attended by the ascending and descending degenerations mentioned above; but these are really secondary results. The grey matter, the spinal roots, and the posterior root ganglia are normal. The vessels in the affected area show thickening of their walls.

It is of importance to note that in most of these cases the degeneration of the posterior and lateral columns is most evident in the mid-thoracic region, and diminishes in degree and extent as the upper and lower limits of the cord are approached. The above-mentioned authors, in discussing the pathogenesis of these lesions, draw attention to their important observation that the distribution of the affection in the white matter is precisely that of the peripheral vessels, the pial supply, and point out how the areas supplied by the anterior median arteries—the anterior horns, adjacent white matter, and Clarke's column—escape.

We have described the above lesions as non-systemic, although it is obvious that in the posterior columns they bear a close resemblance to tabes dorsalis. There are cardinal differences, however, in the primary localization and further spread of the disease which separate it from a true tabes. The term pseudo-tabes might be employed on the clear understanding that the disease is not confined to the posterior columns, but is combined with sclerosis elsewhere.

If we review briefly the type of lesion in the three cases to which we have drawn attention, it is evident that we are dealing with three different degrees of one and the same pathological process. The situation of the degeneration is practically the same in all, especially in the posterior columns; and the late involvement of the fibres in the grey horns is a constant feature. In the cancer cases it is evident that the lesion is characterized by a gradual atrophy and absorption of the myelin sheath. So far as our experience goes, there is no evidence of axis-cylinder change, but the possibility of this occurring in other cases

must be admitted. In the case of Addison's disease the pathogenetic agent is enabled to produce greater damage, for the lesion is not only more extensive, but we find the adventitial lymph sheaths in the posterior columns filled with fatty substance. In addition to this, isolated degenerative patches are found in which the axis-cylinders have suffered sufficient damage to cause a true Wallerian degeneration.

In the subacute combined sclerosis the morbid lesion is even more advanced. In the area of concentration, the mid-dorsal region, the axis-cylinders have been attacked, and the destruction has resulted in ascending and descending degenerations. Above and below the area the lesion is much less acute, and though its limits, above and below, are more extensive than in the cancer cases and in Addison's disease, it is similar in nature. The dissimilarity in extent might be reasonably explained by the fact that the morbid process has acted in a more acute fashion, and its effects have spread farther by diffusion of the noxious agent.

We have already mentioned that these non-systemic cord lesions appear to be caused by some toxic substance in the blood, but a general statement of this nature does not help us to explain the constant and peculiar situation of the lesions. They form a definite group—which, no doubt, includes more members than we have mentioned—whose characteristics make it reasonably certain that some special factor comes into operation in the pathogenesis. We assume that the myelin is attacked by a poison of some kind, and that this, if sufficiently strong, or in action for a sufficient period of time, can injure the axis-cylinder. We have no knowledge relating to the nature of the poison, but the lesions themselves raise an equally important question which is concerned with the mechanism by which these definite areas of the cord are invaded. There are insuperable difficulties in the way of our accepting a "general intoxication" theory without qualification. All the facts are against it. The distribution of the degeneration in the lateral and posterior columns, the localization of the degree of morbid change in the upper part of the cord, the gradual diminution of the atrophic change from above downwards until the lumbar level is reached, and the integrity of the grey matter so richly supplied by the anterior spinal arteries, all make the "general intoxication" theory unacceptable. It may be advanced that the affected areas are composed of fibres whose powers of resistance is less than that of others, but for this assumption we have no foundation in fact. Presumably the poison does not act unaided and indiscriminately, and there are reasons for

surmising that the sympathetic nervous system is, in all likelihood, the intermediary in determining the localization of the lesions. We propose to bring forward evidence in support of this view, derived from recent work in connexion with the autonomic system, as many points in its anatomy, physiology, and embryology, along with some of its relationships to the endocrinic glands, seem to have a direct bearing on the argument before us. We have no accurate knowledge with regard to the part played by the sympathetic system in the causation of central lesions, but the probability of its action in this direction should not be denied for the present, in view of its intimate connexion with the spinal cord and vessels. Neuropathology in the past has provided many data of importance regarding nervous function, and the lesions under discussion, lying as they do almost entirely within the realm of the thoracico-lumbar vasomotor system, suggest that the influence of this upon the central nervous system cannot be ignored. Our experiments affected special parts of the sympathetic system, and produced corresponding localized lesions.

The sympathetic nervous system, though intimately connected with the central nervous system, differs from it in many respects. It controls the visceral and involuntary functions of the body and has been termed by Langley the autonomic system. Its autonomy is only relative however; it has close anatomical and physiological relationships with the central nervous system.

Two ganglionated cords run along the ventral surface of the vertebræ from the atlas to the coccyx, segmentally interrupted by ganglia. Each is divided into cervical, thoracic, lumbar, and sacral portions. The cervical cord contains three ganglia, the thoracic twelve, while the lumbar and sacral portions have four or five each. The upper two or three ganglia of the thoracic cord are usually fused into one called the stellate ganglion.

These ganglia are termed vertebral or lateral: those situated more distally, for example in the cardiac, solar, and hypogastric plexuses, are called pre-vertebral or collateral, and small groups of cells lying more distally still in the course of the nerves before they reach their destination have received the name of terminal ganglia.

Each lateral ganglion is connected with the spinal cord by a grey ramus; only those corresponding to the spinal segments between D1 and L2 inclusive are connected to the cord by white rami also. These white rami, composed of medullated fibres, come from cells in the lateral horn of the cord (the intermedio-lateral tract) and conduct to

the ganglionic cells of the lateral chain. The grey rami are not medullated, they are derived from the cells of the ganglionic chain which they connect with the peripheral organs.

Each white ramus sends off many collaterals and thus is connected with several lateral ganglia. The pre-vertebral ganglia are connected with the spinal cord by the splanchnic nerves, and are concerned entirely with internal visceral organs situated in the abdomen and pelvis.

The thoracico-lumbar connector nerves, that is the white rami communicantes, carry impulses to neurons in the vertebral ganglionic chain which supply (1) motor nerves for the muscles of blood-vessels over the whole body; (2) motor nerves for the musculature of all the sweat glands; (3) the whole pilo-motor system; (4) motor nerves for all unstriped muscle in connexion with structures derived from the segmental duct, that is, the ureter, uterus, and Fallopian tubes; (5) motor fibres to the sphincters of the intestine. The lateral, vertebral ganglia supply motor fibres to the blood-vessels of structures innervated by the segmental nerves, both spinal and cranial, including the central nervous system and the thoracic viscera. The collateral or pre-vertebral chain sends motor fibres to the blood-vessels of the abdominal and pelvic viscera.

There is an afferent system of sympathetic nerves which convey sensory impulses to the central nervous system. They are medullated and pass through the white rami communicantes, and have their trophic centre in the posterior root ganglia from which they run in the dorsal roots to the cord between the levels of D1 and L2.

The existence of vasomotor fibres in the brain has until comparatively recently been steadily denied. The action of adrenalin however has proved the presence of vaso-constrictors in the vessels of the brain, lungs, and heart, although it is admitted that their action is weak, and non-medullated sympathetic fibres have been observed to leave the main mass and proceed along the roots of the spinal cord which they reach by the posterior root especially. From these they pass into the cord membranes to supply the blood-vessels, but none enter the cord itself. Moreover, stimulation of the posterior roots has been observed to cause constriction of the blood-vessels of the dura mater.

The sympathetic ganglionic chain thus appears to be an extensive system of reflexes.[1] It is supplied with afferent and efferent fibres. From the level of D1 to L2 there is a connecting neuron within the

[1] We use the term "reflex" deliberately here.

central nervous system—the intermedio-lateral tract—which completes the arc between the afferent and efferent systems, and this fact, to which we shall return, seems to be of practical significance in connexion with the combined lesions in the cord already described. Another important point which must be kept in mind is that sympathetic action is dependent upon the supply of adrenalin. This point also shall receive further consideration.

It is not possible in view of recent additions to our knowledge of the sympathetic system to consider it as an independent entity. It is now known to be intimately connected both anatomically and physiologically with the ductless gland system. In fact, when we come to study the phylogenesis and ontogenesis of the vegetative system it is at once apparent that its relationship with the adrenal bodies is such that the development of each can hardly be considered separately. Phylogenetic and ontogenetic studies prove conclusively that the sympathetic nervous system, the adrenal bodies, and all chromaffin tissue must be considered as one in relation to the blood vascular system; and our reason for going into some detail in this direction is the importance of this relationship upon the cord lesions under discussion.

From animals low down in the scale to mammals, the close association of adrenal bodies with the sympathetic system has been recognized by many workers. In a primitive form of animal life, for example in the Petromyzon, there are two distinct series of bodies. One is represented by small lobulated structures in the wall of the posterior cardinal veins, of the renal arteries, and of the arteries dorsal to the kidneys. They project into the lumen of the vessels and consist of cylindrical or polyhedral cells containing granules which stain black with osmic acid. These are the cortical or inter-renal bodies. The other series—the chromaffin series—extends from the region of the second gill cleft to the tail, and each strip of tissue runs along the arteries and their branches. These structures bear the same relationship to the veins as the cortical bodies and correspond to the medulla of the suprarenals. These paired suprarenals lie in close contact with the ganglia of the sympathetic chain and contain large numbers of chromaffin cells. When we reach the Reptilia we find a closer relationship established between the cortical and medullary elements; and in birds it is still closer, the latter occupying the meshes of the former.

Mammals alone possess a true cortex and medulla, the latter completely surrounded as a rule. The cortex has the same structure

as its homologues in the lower vertebrates, and consists of rounded groups or columns of cells containing fat-like granules which stain deeply with sudan III, scharlach red, and become blackened with osmic acid. The cells of the medulla have a great affinity for nuclear stains, and with chromium salts may assume any shade from a bright yellow to a dark brown. Cells exhibiting precisely this reaction have been found in the carotid body of mammals; and accessory chromaffin substance is found in any part of the body into which the sympathetic system extends, but especially in connexion with the abdominal sympathetic.

Now physiology teaches us that all chromaffin tissues yield adrenalin, or a similar chemical substance, and that the effects produced by this are almost all such as are produced by the sympathetic system. Comparative anatomy shows also that in addition to the medulla of the adrenal body there are numerous scattered bodies of the same nature in close relation to the sympathetic ganglia and nerves throughout the body. The adrenalin passes by the adrenal veins into the general circulation and assists in maintaining the tone of sympathetically innervated muscle and other tissue; and it is interesting to note in this connexion that the cells of the medulla are derived from the cells of the embryonic sympathetic system. Swale Vincent [11]—from whose comprehensive work we have borrowed extensively—affirms "that the cortex is derived from the mesoderm and the medulla from the same blastema as the sympathetic ganglia is now universally conceded." The intimate relationships between the vegetative nervous system and chromaffin tissue is therefore obvious.

If we look more closely into the development of the sympathetic system its intimacy with adrenal tissue from the earliest is clearly demonstrated.

There are two views regarding the genesis of the sympathetic nervous system, one that it is of mesodermal origin, the other that it is derived from the ectoderm. In a recent and important paper by Bruni [2] the whole question is revived and several facts of fundamental importance added. Observations in the higher vertebrates, and especially in birds, leave no doubt that sympathetic rudiments appear before there are any visible signs of rami communicantes connected with them. Bruni is of the opinion that the first limiting layer is derived from the mesoderm. Near the place where the segmental vessels leave the aorta and at the cranial extremity of the mesonephros small cellular mesodermal accumulations appear. In a short space of

time these, at first arranged segmentally, are gathered into a continuous column and rapidly extend cranially and caudally, forming a dense protoplasmic trabecula. Such formations are particularly evident in the thoracic and abdominal regions. Two other facts deserve special notice. One is that in this mesodermal rudiment droplets of a substance develop possessing a strong affinity for hæmatoxylin. Secondly, simultaneously with the formation of these droplets, or shortly afterwards, neurocytes appear in the lateral branch of each spinal nerve—at least in the thoracic region—which accumulate at a point in the nerve least distant from the mesodermal rudiment and are projected towards it. Bruni is firmly of opinion that the mesodermal rudiment of the sympathetic is originally independent of the ectodermal portion, and adds that the former exerts an attraction on the ventral branch of the spinal nerve.

In a very short period of time the mesodermal and ectodermal rudiments become fused, and as development proceeds some of the trabeculæ (mesodermal) assume intimate relationships with the endothelium of capillaries lying laterally and ventrally to the aorta. The mesoderm then becomes rarefied, shows segmental swellings, and a few cells like posterior root ganglion cells. It is important to note at this stage that the mesodermal rudiment spreads laterally and in front of the aorta in the region where the cœliac and aortico-abdominal plexuses develop. A visceral ramus of each ventral spinal nerve now enters the mesodermal rudiment in the thoracic region: in the abdominal region part only enters, while the remainder expands in the region of the cœliac and abdominal plexuses to establish connexions with the mesodermal polynucleated protoplasmic trabeculæ.

From this stage onwards nerve fibres penetrate the trabecular mass freely, which thus becomes linked up by rami communicantes to the spinal nerves. With the advancement of development the polynucleated masses become more scanty, save in the region of the future cœliac and abdominal plexuses where they undergo a decided increase. These masses are permeated by nerve fasciculi, and are in intimate contact with the endothelium of the large capillaries. Still later in development the mesodermal rudiment, having attracted the fibres and cells of the spinal nerve destined to supply the true sympathetic elements, and having established connexions with the endothelium of the vessels, in part becomes transformed into a fibro-cellular cord, while a portion in the region of the cœliac and abdominal plexuses develops into the chromaffin formations which constitute the paraganglia and the medullary substance of the suprarenals.

There are some special points in connexion with the cervical sympathetic which deserve notice. Here the primary limiting layer gradually becomes less intimate with the spinal nerves and establishes connexions with the cranial nerves, especially the tenth, which in mammals contributes cellular elements early to the sympathetic cord. The superior and middle cervical ganglia are derived from a non-segmented cord, are not supplied with neurocytes by spinal nerves metamerically, but by elements which come up from the thoracic region and down from the ganglion nodosum of the vagus nerve. This is an important point, and Bruni mentions it in relation to the observations of His, Kuntz, and Abel, according to whom elements from the ninth and tenth cranial nerves supply supra-diaphragmatic plexuses of the sympathetic, especially the cardiac plexus and ganglia. Studies in comparative anatomy show that as we ascend the animal scale the components of the cervical ganglion tend to come progressively less from the spinal nerves and more from those of the sympathetic portion of the vagus.

An examination of the data obtained from a study of the sympathetic system provides us with certain facts which, if they do not afford a complete explanation of the lesions in the conditions mentioned above, at least are of sufficient importance to merit attention, and suggest a problem worthy of further investigation. There can be no doubt that the localization of these lesions in the central nervous system is not caused in a haphazard fashion in the course of a general intoxication. Such a definite localization as we have seen in the area of pial supply can be, in the cord at least, correlated with the spinal distribution of the thoracico-lumbar sympathetic system. This we have seen possesses central neurons (the intermedio-lateral tract) which send efferent fibres, preganglionic fibres, to the ganglionic chain, and receives afferent fibres, all, or nearly all, of which run into the posterior root ganglia—their trophic centre—and onwards into the cord by the posterior roots without entering into direct relationships with the sympathetic ganglia. The stimulus which these afferent fibres communicate must reach, therefore, the central nervous system before transmission to the periphery. We must conclude from this that in the sympathetic ganglionic chain there is no true reflex arc, or in other words that it cannot subserve reflex action without the intervention of the cerebro-spinal axis. But experiment has shown that in the sympathetic chain there are pseudo- or axonal-reflexes in which no afferent fibre is involved, and when a stimulus is applied to an axis-cylinder it can be

transmitted by one of its collaterals to another cell or another ganglion as each preganglionic fibre sends collaterals to many ganglia.

Langley's work shows, however, that the sympathetic ganglia cannot maintain tone apart from the central nervous system, and the consensus of opinion seems to be that the ganglia merely act as reinforcing centres for stimuli from the central axis. But in the afferent and efferent systems of the spinal sympathetic centres and their connexions with the chain of ganglia we have all the elements of a true reflex arc, and the distribution of the spinal cord lesions is practically within the realm of this arc.

The involvement of the cervical segments does not contradict the argument, for, though the thoracico-lumbar mechanism lies within the limits of D1 and L2, it should be remembered that the lower half of the cervical cord is supplied by the ramus vertebralis composed of grey fibres derived from the stellate ganglion, which consists in a fusion of the first two or three thoracic ganglia. There are strong anatomical reasons, therefore, for the hypothesis that some disturbance of the sympathetic system may be held responsible for the localization of the atrophic and sclerotic changes, as they are only found in the vascular areas known to be under sympathetic control, i.e., those supplied by the pial vessels.

It is difficult to understand why the lower cervical and upper dorsal regions are most affected, and we have no explanation to offer. In all probability this problem, amongst others, involves an elucidation of the complex reflex paths in the sympathetic chain. Obviously these are not so direct as those in the peripheral spinal nerves, a point well exemplified by such common examples as the complex course of the dilator fibres of the pupil, the referred pain of visceral disease, and the unilateral malar flush so frequently seen in pneumonia. That the sympathetic system, however, comes into action in physiological and pathological conditions in the central nervous system seems to find additional support from the spinal cord lesion found in Addison's disease, whose syndrome is that of adrenalin inadequacy. Here we have muscular hypotonus and fall in blood-pressure generally, from which one can argue vaso-dilation in the pial supply of the cord.

We would suggest, therefore, that the lesions we have described are due to some interference with the thoracico-lumbar sympathetic reflex, caused possibly by pathological stimuli, or by the absence of substances which maintain its balance. This results in dilatation of the pial vessels whose permeability is thus increased. Hence the diffusion of

noxious substances amongst the nerve fibres is facilitated, resulting in a progressive and ever-widening circle of atrophy and sclerosis.

If we are correct in the assumption that the organic cord lesions we have described are the result of some disturbance of the sympathetic system, then it would seem equally legitimate to suggest that certain so-called functional disturbances of the central nervous system may owe their origin, or if not that, their tendency to recurrence and permanency to the same mechanism; for, as we have seen, the sympathetic system is intimately linked up with the central nervous system, has no true autonomy, and there are anatomical paths which provide for a constant interaction between both.

Stimuli must be passing constantly from the sympathetic to the central nervous system, as there are special sense organs in the viscera and a definite sensory afferent path; and although these stimuli do not pass the threshold of consciousness normally, one cannot deny that they exercise physiological effects, knowing that under abnormal conditions they evoke pain. We must admit, therefore, that the stimuli from the sympathetic system exert an influence upon the brain under normal conditions, and play an important part in mental activity. In all probability stimuli coming from the vegetative organs to the brain, where they excite bodily sensations and instincts in consciousness, are of as great importance as those derived from the external world. And there is another point which must be taken into consideration. The relations which the sympathetic chain has with the vascular system and the ductless glands add very considerably to its functional importance in physiological and pathological conditions, so that in considering its influence on the central nervous system we have not only the effect produced by stimuli to take into account, but that through the vascular and endocrinic systems as well.

The precise relationship of the vascular system to the nerve-cells, and the mechanism by which the functional activity of these highly specialized elements is controlled, is still very obscure. Some modern workers are of opinion that the neuroglia plays some part in the process, and though the views advanced are not yet quite convincing, still with our knowledge so scanty as it is at present we must give them due consideration.

Achúcarro [1] considers that all the protoplasmatic neuroglia functionates as an interstitial gland which acts on the nerve elements and on the blood, contributing by means of special hormones to the endocrinic harmony of the organism. This view is based to a large

extent on the presence of a foot-like process at the peripheral end of the neuroglia fibre which forms a connexion with the blood-vessels, and on certain embryological data.

The primitive neuroglia is represented by the ependyma, and, as development proceeds, the "neuroglial-ependymal" elements pass into the depth of the tissue. These embryonic neuroglial cells develop more rapidly in those ganglia which have acquired the greatest morphological and physiological importance. As the central nervous system thickens, and acquires a rich vascular network, the connexion between the neuroglia and blood-vessels becomes progressively more intimate, and Achúcarro advances this in support of his hypothesis that the neuroglia is a glandular vascular system. Cajal also is of opinion that there is a nutritive relationship between the neuroglia and the nerve-cell. When the nerve-cells are nourished from the ependymal space, they remain in that situation, and are unipolar; but when the vascular network is established, and the neuroglia becomes autonomous, then the neurons migrate, and become multipolar. It would appear from these authors that the neuroglia, under normal conditions, neutralizes noxious substances coming from the vessels, and destroys catabolic products from the nerve-cells, thus constituting a constant chemical rejuvenator, to a certain extent, in the substance of the nervous system. Achúcarro then pushes his theory still further, and applies it to the mechanism of the emotions. Granted, he says, that there is an indirect connexion between the nerve-cells and the vascular system, the neuroglia considered as an internal secretory gland could take part in the emotional mechanism. Recent researches, he continues, especially those of Cannon, have shown that in emotion not only is there a dynamic repercussion transmitted from the nerve elements, but there is also a true humoral repercussion expressed by an increase of glucosides and adrenalin in the blood, indicating hyperactivity of the adrenals. In this connexion Crile has drawn attention to an increased activity of the thyroid in emotion. Achúcarro thinks, therefore, that he is justified in advancing the theory that the protoplasmatic neuroglia, on account of its structure, relationships with the vascular system, and intimacy with the nerve-cells, can at certain times of nervous activity pour hormones into the blood which provoke other endocrinic manifestations with which emotionalism is associated.

Lugaro [3], criticizing Achúcarro's work, draws attention to its psycho-physiological nature in relation to the somatic humoral mechanism of the emotions. He points out, however, that emotion can

be awakened purely dynamically through the nerve paths. Emotional phenomena take place with such rapidity that only nervous transmission from the brain to the periphery, and vice versa, could bring them into play. Were the emotional mechanism entirely dependent upon internal secretion, the emotion would occur slowly and last an excessive time. Lugaro notes that all the phenomena manifested during an emotion, or immediately afterwards, are not an integral part of its mechanism. It is conceivable that they could be for the most part purely collateral effects, devoid of any biological utility and perhaps, by their overflow, even damaging. He suggests the investigation of the relationships between certain conditions of disturbed hormonic equilibrium and the variations which they induce in the excitability of the nervous elements, especially those of the visceral system. Possibly for each type of disturbed equilibrium there may be an excessive facility or an abnormal inhibition of certain emotions. For example, there are the anxious apprehension in Graves's disease, and the phlegmatic character in hypothyroidism. An ideal affective equilibrium, ideal character, and a perfectly normal emotional state only exist with perfect hormonic equilibrium; and if lively emotions, especially when prolonged, disturb the hormonic balance they acquire greater importance inasmuch as an abnormal emotional state arises through disturbed humoral equilibrium. It is along such lines that Lugaro thinks we shall arrive at a knowledge of the physiology and pathology of the affections, and perhaps even find a rational somatic therapy of the dysthymiæ.

There is an interesting paper by Von Monakow [5] in which he enters a plea for the material basis of the sentiments and emotions. He is of opinion that the material basis of the sentiments ought to be regarded as chemical, not as anatomical or morphological. The chemistry of the blood and endocrinic glands comes into play as a varying and most important factor. The chemical composition of the blood is of cardinal importance for the sentiments; for sensation, motion, and orientation in time and space, it is—within physiological limits—of less importance. Even as low down in the animal scale as Vermes, there exists, in the cells of Leydig, an organ homologous with the endocrinic glands. In the human fœtus there are at the second month indications of the suprarenal capsule, which are intimately connected with the sympathetic ganglia; and the extreme sensitiveness of the sympathetic to pharmaco-dynamic action has been demonstrated by adrenalin, pituitrin, cocaine, nicotine, atropine, &c. Cannon and

Asher have shown that psychic excitement determines, through the sympathetic paths, a hypersecretion of adrenalin into the blood. The internal secretory glands, therefore, influence the nervous system in general, and the sympathetic in particular, and so provide a diffuse mechanism which regulates the vegetative or instinctive life of the organism. Thus the way is paved for elective chemical actions to create, on the exhibition of special stimuli, a favourable or inhibitory influence, and determine, amongst a conflict of stimuli, the appearance of a certain sentiment. Von Monakow then proceeds to discuss the epochal development of the sentiments in man and his conclusions are of the greatest interest. He says that, broadly speaking, the evolution of the sentiments cannot be placed in clear relationship with the phases of anatomical development. All we are justified in saying is that the primordial sentiments ought to have a more solid organic basis than those of later growth, and therefore under morbid conditions their resistance to the tendency to dissolution is greater. He supports the psycho-analytical school who ascribe great importance to the psycho-genetic factor in the functional psychoses, neurasthenia, obsessions, and hysteria, but tempers their views by an unqualified admission of somatic factors. While he readily grants the frequent incidence of degeneration as a predisposing factor, great stress is laid upon the biochemical, organic, or somatic factor, that is to say, one absolutely apsychic. For example, moral trauma, severe psychic conflict, unsatisfied strong instinctive tendencies, disturb, through the sympathetic system, the endocrinic glands; and thus changes arise in the blood, which, combined with prolonged psychic stimuli, create nervous instability, resulting in neurasthenia, hysteria, phobias, and hypochondriasis.

"Evidently then," as Lugaro remarks in his criticism [4], "the nervous system and the endocrinic glands act as one under certain circumstances and constitute the basis of many changes in normal psychic life; both are naturally more operative in certain pathological states, which psychologists have tried to explain by fantastic hypotheses. Between moral trauma which arises from a psychic cause and its psychopathic effects there are a series of phenomena which no doubt come under the term 'unconscious.' But the 'unconscious' is not necessarily that of the psycho-analyst, psychic unconsciousness; it is conceivably the result of chemical phenomena as unconscious and apsychic as any other."

The psycho-neuroses of the war provide an ample field for the application of all the above data, and demonstrate conclusively how

disturbance of the sympathetic mechanism, of the endocrinic glands, and morbid emotional conditions, combine to bring about pathological psychic and nervous phenomena. Doubtless these three factors do not act separately. From their physiological intimacy we can hardly escape from the conclusion that all three act together.

Pathogenesis is invariably a difficult problem and especially so in the case of psychoneuroses. As Pighini [9] points out in his discussion of the clinical symptoms and pathogenesis of emotional psychoneuroses, we still know little of normal psychic processes, and of their connexion with other organic processes in the body. The physiology of pleasure, pain, and of the emotions generally shows us, however, that these psychic states are associated constantly with somatic repercussions which are maintained especially by the sympathetic nervous system; but much obscurity exists regarding the manner and path of conduction by which these come about. Pighini is an adherent of Bechterew's view, that in the cortex there are so many successive sensory-motor regions with psychic functions. Each of these regions consists in a receptive centre which is in intimate functional and anatomical connexion with a neighbouring efferent centre, thus forming an organic neuropsychic unity, e.g., optico-motor, acustico-motor, tactile-motor. Sympathetic centres are intimately connected with the above and take part in all psychic and psycho-sensorial processes, and thus it is easily conceivable how the sympathetic system becomes involved in disturbed neuropsychic activity by direct transmission from the original site of injury in the sensory motor cortex. For example, the hyperexcitability of the cortical visual or auditory zones, induced by shock, may be diffused to the limiting efferent regions and onwards to the inferior centres in the mesencephalon, medulla, and cord. Hence there arise dilatation of the pupils, nystagmus, cardio-vascular and vaso-motor phenomena, and other symptoms.

The more extensive the neuropsychic zone excited by emotional trauma is, the more accentuated and complex is the morbid repercussion in the sympathetic sphere. These are always more or less accentuated, and are an integral part of the syndrome of traumatic psychoneurosis. The purely psychic symptoms of stupor, acute confusion, hallucinatory delirium, excitement, and exaggerated emotional tone come on as a rule before the somatic symptoms due to involvement of the sympathetic and endocrinic systems; and Pighini is of opinion that this implication assumes, secondarily, the preponderating part in the morbid process and prevents recovery of the disturbed central function.

The somatic symptoms, therefore, are worthy of the most minute examination, seeing that they may prove to be the key to the correct interpretation of the morbid state.

In regard to the sympathetic system the most prevalent signs are those of hypofunction. It must be granted, however, that it is often a difficult matter to decide whether the disturbance is due to hypofunction of one system or hyperfunction of its antagonist. For example, in a case presenting dilatation of the pupil and tachycardia one has to determine whether these depend upon heightened tone of the sympathetic or diminished tone of the antagonist third or tenth nerves. Pharyngeal and laryngeal anæsthesia, paresis of the vocal cords, tachycardia, asthma, frequent vomiting, the absence of the oculo-cardiac reflex and its inversion, all point to vagus hypotonia; while bladder trouble points to involvement of the pelvic nerve.

There are other symptoms indicating involvement of that part of the sympathetic in close relationship with the endocrinic glands. These are dermographism, hyperidrosis, epigastric impulse from the aorta, exophthalmic goitre, and erythromelalgia. Tremor and clonism accompanied by tachycardia, marked asthma, slight hyperthermia, hyperidrosis, and psychic hyperirritability are common. Pighini attributes those symptoms to endocrinic disturbance, and is inclined to give preference to an altered functional state of the thyroid gland. He has found that the thyroid gland reacts readily to sympathetico-cortical trauma, and, having undergone change in function, in turn it induces morbid complications amongst other units of the complex endocrino-sympathetic system. This inevitably leads to a reduction of hormone influence and consequently autonomic hypotonia, whose symptoms amongst others are tremor, Addison's disease, Raynaud's disease, emotional hyperidrosis, diabetes mellitus, and angioneurotic eruptions. All these conditions have been observed to follow violent mental suffering.

There are certain neurological conditions incidental to war wounds, such as trophic disturbance in limbs, osseous and muscular atrophy, hypertrichosis, hyperidrosis, œdema, hypothermia, anæsthesia, paræsthesia, paresis, causalgic pain, and other symptoms which are not referable to lesions of the sensory or motor nerves, but rather to concomitant sympathetic disturbance. These symptoms according to Pighini are true traumatic tropho-neuroses of reflex origin. It would seem therefore that the function and conductility of sensory and motor nerves can be injured by vasomotor changes.

From all the above it is quite evident that there is sufficient justification for the suggestion that the sympathetic nervous system, though in physiological control of the involuntary functions, plays a much greater part in central nervous processes than has been previously admitted. However one may look at the problem, certain facts emerge which prove the close interdependence of the vegetative and central nervous systems.

The situation of the experimental lesions in the cord and brain noted above supply us with this fact, that these are the result of disordered nutrition and occur in the regions of the central nervous system whose vessels are under sympathetic control, that is, in the area of pial supply; and the remarkable distribution of the spinal non-systemic lesions in the three clinical entities considered affords additional evidence of the operation of the sympathetic factor. At least one must attach no small significance to this fact, that these lesions in the cord occur within, and attain their maximum intensity in the upper part of, the spinal area from which the white rami are projected to the sympathetic chain, and pass the bounds of this area to a slight extent only. But when we come to study the embryology of the sympathetic system and its intimacy with the endocrinic glands, and their joint physiological effects upon the central nervous system and *vice versa*, our prior arbitrary division of these into separate organs —in the physiological sense—becomes manifestly absurd; and the clinical evidence substantiates this view.

It is apparent therefore that in nervous diseases, and in those especially which concern the cerebrum, we must in future study not only the more prominent symptoms dependent upon disturbed function of the central organ, but also the collateral symptoms arising from disturbance of all the peripheral organs intimately connected with it. Anatomy, physiology, embryology, psychology and clinicial neurology indicate clearly that the problem cannot be solved by a narrower programme.

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CONDUCTION IN PERIPHERAL NERVE AND IN THE CENTRAL NERVOUS SYSTEM.

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INTRODUCTION.

WITHIN recent years the process of excitation and conduction in the peripheral nerve-fibre has been analysed with considerable accuracy and our conception of the nervous impulse has become far more definite. This analysis is inseparably connected with the name of Keith Lucas, and it is grievous to speculate how far he would have extended it if he had lived. The results so far attained may be considered from two distinct points of view. In the first place they represent the groundwork of an attempt to express a function of the living cell in terms of physics and chemistry. They are studies in cell physiology rather than in neurology, and though the particular function investigated happens to be that of nervous conduction, this function was chosen only because it happens to be very highly developed in certain specialized cells and therefore susceptible to much more accurate measurements than other functions such as those of assimilation or secretion. The investigation of the temperature coefficients of the different phenomena in nerve [5], [27], the characteristics of the electric current required to excite [29], the relation of the size of the impulse to the rate of conduction [6], [21], and similar problems are all directly concerned with this aim and their results form a body of evidence on

which any theory of nervous activity must be judged. They have already led to theoretical results of some interest [32], but any advance on these lines must needs be a slow business, since it is limited by our very imperfect knowledge of colloidal phenomena and, although this need not deter us, it may turn out in the end that the vitalists are in the right when they assert the impossibility of describing vital processes in terms of the laws of mechanics.

But the analysis of conduction and excitation in the nerve-fibre may be considered from an entirely different point of view, that of the neurologist who is concerned not with the physics and chemistry of the nervous impulse but with the mechanism by which the impulse is made to serve a useful purpose in the body, the mechanism of the reflex arc and of the central nervous system in general. Unless we know the chief characteristics of the nervous impulse in simple conducting tissues, such as the peripheral nerve-fibre, it is waste of time to speculate on the nature of inhibition, summation, and all the other modifications of nervous activity which make up the work of the central nervous system. In this sense a knowledge of the behaviour of the impulse in a single nerve-fibre must form the basis of all neurology which is not concerned exclusively with the anatomical and functional arrangement of different tracts and cell stations in the cord and brain.

As will be seen, the analysis of peripheral conduction reveals several principles which are of direct importance to neurology. These principles have been outlined in the following article, which is little more than a summary of Keith Lucas's work on the nervous impulse [34]. It must be understood that the extension of our knowledge of peripheral conduction to cover the case of the central nervous system as well can only be justified as a forecast which may need a good deal of modification when the evidence is more complete, but it is at least a forecast which may suggest future lines of attack.

Chapter I.—The Identity of the Impulse in the Nerve-muscle Preparation and in the Intact Nervous System.

As most of the evidence has been derived from experiments on the classic sciatic-gastrocnemius preparation of the frog, it is as well at the outset to consider how far we are justified in assuming that the impulses set up in an isolated nerve by electric stimuli applied to the nerve trunk are identical with the impulses passing in or out of the central nervous system in the intact animal. The point is so important that it merits discussion in some detail.

Clearly, if what we call the nervous impulse in an isolated muscle-nerve preparation is an artificial effect quite unlike anything that happens in life its investigation will not help us much. As a matter of fact this extreme position is seldom advocated and there is abundant evidence that impulses identical with those studied in isolated nerve do form a large proportion of the impulses which occur under normal conditions in the body. The electrical stimulation of motor and sensory nerves in the living subject produces effects which differ in no way from those due to normal reflex activity; the rates of conduction are the same and the muscle gives the same oscillating electric response. Much of this evidence has been discussed at length by Piper [37], but the most conclusive proof comes from the recent experiments of Forbes and Gregg [18]. In these experiments it was possible to photograph the changes of potential in a motor nerve forming part of a reflex arc and called into activity by stimulating the appropriate sensory nerve. Taking into account the slight differences introduced by variations in the length of the conducting path, &c., it was found that the records of reflex activity showed electric responses which did not differ in any way from the electric responses obtained by direct stimulation of the isolated nerve. Thus we can scarcely doubt that the active contractions in a reflex arc are called up by nervous impulses of the same nature as those which form the subject matter of the classical muscle and nerve physiology. But it may reasonably be questioned whether there are not other forms of conduction in the intact nervous system quite unlike the form which can be studied in isolated nerve. It must be admitted at once that we know very little of the nature of conduction in non-medullated nerve and we must be content to regard the action of the autonomic system as outside the scope of the present inquiry. However, the real difficulty arises from the fact that we do not know whether the tonic postural contraction of voluntary muscle is controlled by the same nervous mechanism as that which regulates the active phasic contraction. The evidence on this subject is still very inconclusive. Undoubtedly there does exist in certain muscles, e.g., those operating the claw of the crayfish, a tonic mechanism which enables the muscle to remain shortened for long periods without appreciable loss of energy. This steady contraction appears to be entirely different from the tetanus produced by repeated stimulation of a nerve leading to the striated muscle of a vertebrate. Whether the same type of mechanism comes into play in such conditions as decerebrate rigidity, or indeed in all forms of postural contraction, is

still an open question. Many attempts have been made to show that voluntary muscle contains two distinct contractile mechanisms for the twitch and for the tonic contraction supplied by two sets of nerves, medullated and non-medullated, or by two forms of nervous impulse. If this is so it is clear that the production (and inhibition) of tone must be due to a mechanism quite distinct from that studied in the muscle-nerve preparation. The theory owes most of its development to Bottazzi [15], who identifies the two contractile mechanisms with the sarcostyles and sarcoplasm of the muscle; it certainly offers an easy way out of the many difficulties which arise when we attempt to compare the twitch and the tetanus of the frog's gastrocnemius with the nicely adjusted movements of the living body, but it does so by postulating a mechanism of which we have as yet no direct proof and of a nature sufficiently vague to make disproof very difficult. For a detailed account of the evidence the reader must be referred to the papers of Bottazzi, Roaf [38], Langelaan [23], Dusser de Barenne [13], &c. The question will be referred to again in connexion with inhibition. For the present, it is justifiable to conclude that the impulses which govern the rapid contractions of striated muscle in the body are identical with those which can be reproduced experimentally in isolated nerve, but we must admit that there may be other kinds of nervous impulse of whose nature we are still quite ignorant.

Chapter II.—The Chief Characteristics of the Impulse in Peripheral Nerve.

§ 1.—*The All-or-None Principle.*

When the frog's sciatic nerve is stimulated mechanically, electrically or chemically, the gastrocnemius muscle contracts after a short but appreciable interval. The interval is longer when the stimulus takes effect at some distance from the muscle, and shorter when the distance is less. By measurements of this kind it can be shown that the stimulus sets up some disturbance in the nerve which travels down it at the rate of about 28 metres a second, and leads eventually to the contraction of the gastrocnemius. This disturbance is spoken of as the nervous impulse. Its nature is unknown, and the only direct accompaniment of it which can be detected with certainty is the electric response. The nerve in the region stimulated becomes electrically negative to other points on the nerve, and a "wave of negativity" spreads out in both

directions with a velocity equal to that of the nervous impulse. There is possibly an evolution of CO_2 at the same time, but this is still rather doubtful [44].

Now, if two stimuli, separated by a short interval of time, are sent into the nerve, two nervous impulses are set up, two electric responses pass down the nerve and the muscle gives a summated contraction due to the fusion of two twitches. However, if the interval between the stimuli is reduced until it is of the order of 0·003 second, the second stimulus fails to set up any nervous impulse; the second electric response is absent and the muscle gives a single twitch only. In the same way if the stimuli are repeated with sufficient rapidity the nerve may fail to respond to every second or every third stimulus, and the number of nervous impulses may be only a fraction of the number of stimuli. This fact is of fundamental importance; it shows that the activity of the nerve-fibre cannot be continuous, and that conduction must always proceed by means of a series of discrete impulses which cannot follow one another at less than a certain interval. This interval is known as the refractory period; it varies with the temperature, the nature of the fluid surrounding the nerve, &c., but on the whole it is remarkably constant when the external conditions are not changed, and it is therefore extremely amenable to experimental analysis.

The mere existence of the refractory period leads to a very interesting conclusion as to the relation between the stimulus and the impulse [4]. It can be shown that the action of the external stimulus is to produce a local disturbance of a nature quite different from that of the nervous impulse; this local change takes a certain time to develop, and it must reach a certain intensity before the nervous impulse is set up at all; if it does not reach this intensity it subsides gradually when the stimulus ceases and nothing further takes place. Once the requisite intensity is reached, the nervous impulse is set in motion and the tissue enters into the refractory state. A second stimulus of the same strength occurring very soon after the first may increase the local change, but it will not be able to set up a second nervous impulse. Now if we reduce the time interval between the two stimuli to zero, the two acting together will have double the strength of the single stimulus; but, as before, the nervous impulse will be set up as soon as the local change reaches the required intensity and any further increase in its intensity will be without effect. So that, provided the stimulus is strong enough to set the impulse in motion, a further increase in its strength will not have any effect on the intensity of the impulse; in other words, the intensity

of the impulse does not depend on the strength of the stimulus which sets it in motion. The process may be compared to that of firing a rifle by pressing the trigger. A certain force has to be applied to the trigger before anything happens, but the force may be increased indefinitely without causing the bullet to travel any faster.

It is, of course, well known that an increase in the strength of stimulus applied to a motor nerve trunk will lead to an increase in the force of contraction of the muscle, but here we are dealing with a structure composed of many nerve-fibres, and many muscle-fibres, and the increased contraction might be due simply to an increase in the number of muscle-fibres thrown into action. By experimenting with preparations containing very few nerve and muscle fibres Lucas [27] has shown that this is the case, and his results have been confirmed recently by Eisenberger [17]. If the muscle-fibre contracts at all it does so with a constant force which is independent of the strength of the stimulus. Thus there is an all-or-none relation between the strength of the stimulus and the contraction of the muscle-fibre. However, this gives us no information about the nervous impulse itself; we are dealing only with the beginning and end of a very complicated series of events, and it might be that the nervous impulse varied with the stimulus, even though the muscular contraction did not. Before considering this it will be necessary to arrive at some more definite understanding of what we mean when we speak of the intensity or size of the impulse.

From the point of view of the physics and chemistry of nervous conduction, the intensity of the impulse would mean the intensity of the change of state which spreads down the nerve-fibre. But we do not know what this change of state may be, and although it is accompanied by (and possibly identical with) the electric response, we do not know the exact relation between the two. Moreover, there are great experimental difficulties in measuring the electric response of a single nerve-fibre, and the response of a complete nerve-trunk will depend on the number of fibres in action as well as on the intensity of the change in each fibre. For this reason the measurement of the electric response in a nerve does not give much information as to the intensity of the impulse in each fibre, although such measurements certainly suggest that the intensity is independent of the strength of the stimulus [22]. However, from the present point of view, what really concerns us is not so much the intensity of the physical and chemical disturbance which is the basis of the nervous impulse, but the capacity of the impulse for propagating itself successfully down the nerve-fibre and

overcoming any obstacles it may encounter in its passage through the central nervous system. In this sense it is legitimate to define the intensity of the impulse as meaning its capacity for conduction, and this capacity can be measured without much difficulty.

When a portion of the nerve-trunk is exposed to the action of a narcotic such as alcohol (or, indeed, to any set of conditions which leads to a depression of function without actually killing the fibres), it is found that a stimulus applied near the distal end of the narcotized tract will produce a contraction in the muscle, whereas one applied at a greater distance away will be unable to affect it, in fact there will be a limit to the length of narcotized fibre which can intervene between the point of stimulation and the muscle if the nervous impulse is to be conducted successfully [49], [20]. As the depth of narcosis is increased, the maximum distance through which the impulse can be conducted becomes smaller and smaller, and this holds good whether the stimulus takes effect within the narcotized region or on the normal nerve outside it on the far side from the muscle. As the whole of the narcotized tract is in the same state at any given stage in the narcosis, the facts can only be explained by supposing that the impulse becomes progressively less and less able to travel as it passes through the narcotized region. If it has only a short distance to go it will be able to pass the narcotized area and reach the normal fibre again, but if the distance is longer its ability to travel will be diminished to such an extent that the impulse will be extinguished completely. In other words, the intensity of the impulse suffers a progressive decrement as it passes through the affected region; when the depth of the narcosis is slight the decrement is small and the impulse can travel a long distance without extinction; when the depth is greater the decrement is more pronounced and the impulse is extinguished before it has gone very far. Evidently this furnishes a means of measuring the intensity of the impulse in terms of its ability to travel; we have only to arrange that the impulse whose intensity is to be measured shall pass through a region of progressive decrement, and the intensity will then be proportional to the distance which can be travelled in this area before complete extinction. This method is of great value in many ways, and it can be applied very simply to decide the question whether the intensity of the impulse varies with the strength of the stimulus or not. A muscle-nerve preparation is set up so that it can be excited by stimuli of variable strength at a point near the origin of the nerve. Between this point and the muscle is interposed a narcotizing chamber. The threshold

stimulus (i.e., the stimulus which is just strong enough to give a muscular contraction) is first determined and the narcotic is then allowed to act gradually until the moment when this stimulus has just ceased to affect the muscle. At this moment the decrement suffered by the impulse in the narcotized area will be just great enough to extinguish it before it can pass out into the normal nerve beyond. However, an impulse of greater intensity should be able to pass through without extinction, and if a stronger stimulus is able to set up an impulse of greater intensity we should find that a stimulus two or three times as strong as the threshold would still be able to produce a contraction in the muscle. As a matter of fact, it is found that stronger stimuli have no such advantage; at the moment when conduction fails for impulses set up by a weak stimulus it fails also for those set up by stimuli many times as strong. This experiment [43], [25], [3] proves the conclusion already deduced from theoretical grounds, namely, that the strength of the stimulus does not affect the intensity of the nervous impulse which it sets up, provided only that the stimulus is strong enough to set up an impulse at all.

This shows that there is an all-or-none relation between the stimulus and the nervous impulse, but it does not show that the nerve-fibre cannot transmit impulses of different intensities if these can be sent into it by some means other than direct stimulation of the fibre itself, e.g., from the central nervous system. Evidently a narcotized fibre can transmit impulses of different intensities, though in this case the intensity does not remain constant as the impulse travels down the fibre; again, as will be seen later, the intensity of the impulse may vary with the state of recovery of the fibre. Thus the intensity is not absolutely invariable under all conditions, but this does not settle the question whether it is variable in the normal fibre. This point can be tested by much the same method as that described above. An impulse is made to pass through a narcotized region so that its intensity is reduced, and it is then allowed to emerge into the normal fibre beyond. Does its intensity remain smaller than it was at the beginning or does it recover to the normal value as soon as it has left the narcotized area? Its intensity is measured by determining its ability to pass a second narcotized tract and comparing it with that of an impulse which has been set up by stimulation at some point between the two narcotized tracts. This impulse will not have undergone any reduction in intensity when it reaches the second tract, so that its behaviour may be taken as an index of the normal. It is found that as great a depth of narcosis

or as great a length of narcotized fibre is required to extinguish the impulse in this second tract whether it has been reduced by passage through the first tract or not. Thus the impulse must recover its normal intensity again when it passes out of the region of decrement into normal fibre, and it is therefore impossible to vary the intensity of the impulse in normal fibre by compelling it to pass through a region of imperfect conduction where the intensity will be reduced, the change in intensity is confined to the affected region and does not persist when the impulse emerges into normal fibre again [1].

These results are best expressed by the statement that in a normal nerve-fibre, where the impulse is not conducted with a decrement, the intensity of the impulse at any point depends only on the local condition of the fibre at that point and not at all on the previous history of the impulse before it arrives there. It does not depend either on the strength of the stimulus which set the impulse in motion or on the amount of reduction which the impulse may have suffered in regions of decrement as it passed down the nerve.

This is generally known as the "all-or-none" principle in nervous conduction. The foregoing is only a short abstract of the evidence on which it is based, but a more complete account may be found in the monograph on nervous conduction by Keith Lucas.

So far we have considered the impulse as an isolated event occurring in resting nerve, and in this case the intensity appears to be a fixed quantity, but in life it is unlikely that impulses ever occur singly except perhaps in the simplest of reflex actions. Consequently we have to consider how the impulse may be modified if it forms part of a series and passes through tissue which is still recovering from the effects of a previous impulse.

§ 2.—*The Recovery after the Passage of an Impulse.*

As we have seen, the immediate effect of the impulse is to make the nerve-fibre absolutely inexcitable and unable to conduct a second impulse. In the frog's sciatic at 15° C. the absolute refractory period lasts for about 0·003 second after the moment when the first impulse passes through the region under investigation. After this the excitability returns gradually. At first a very strong stimulus is needed to set up a second impulse and a weaker stimulus has no effect at all, even though it is several times as strong as the normal threshold, but as the interval between the two stimuli is increased the necessary strength of

the second stimulus is gradually reduced, until at about 0·015 second it has fallen to the threshold value again. Following this comes a period of enhanced excitability in which the impulse can be set up by a stimulus weaker than the normal threshold for resting nerve [10]. In the frog's sciatic the increase of excitability is not very great and it is often difficult to detect at all, but there is no doubt that it exists, and in the nerve to the crayfish's claw the excitability may be increased to as much as 125 per cent. of the normal [33]. This period of increased excitability probably lasts until about 0·1 second after the passage of the impulse, though the end-point cannot be determined with much accuracy.

The changes of excitability are accompanied by parallel changes in the intensity of the impulse which can be set up during the different stages of recovery. During the absolute refractory period a second impulse cannot pass at all, even though it has been set up in some region where recovery is more advanced. During the stage in which the excitability is returning to normal the intensity of the second impulse is at first very small. As the interval between the first and second impulse is gradually increased by timing the second stimulus later and later, the intensity gradually rises until at about 0·015 second it is fully equal to that of the first impulse, which has, of course, the normal value for resting nerve. During the period of enhanced excitability the second impulse is greater than the first and this increase lasts for about the same length of time as the increased excitability. As before, the intensity of the second impulse is measured by determining the distance which it can travel in a region of decrement before it is completely extinguished and comparing this with the distance travelled by the first. When the second impulse is set up very soon after the first it is extinguished after a very short distance, but if it is set up during the period of increased excitability it will travel through a greater distance than the first.

Thus the whole course of recovery may be divided into three stages. There is first of all the absolute refractory period when all activity is abolished, then the period of depressed activity in which the nerve conducts an impulse of small intensity and needs a very strong current to excite it, and from this there is a gradual transition to the final period of enhanced activity when the excitability is greater than the normal and the intensity of the impulse also greater.

It is to be noted that for any given stage of recovery the intensity of the impulse which can be set up is still independent of the strength

of the stimulus, provided this is great enough to set it up at all; also that the impulse is not conducted with a decrement although it may have an intensity less than the normal. As long as the impulse does not pass into regions where the state of recovery is altered it remains of the same intensity, but the intensity may be reduced by causing it to pass into a region at a lower temperature where recovery takes place more slowly, or increased by leading it into a region at a higher temperature where the recovery is more advanced.

The results so far described show that the intensity of a single nervous impulse, defined as its ability to pass a region of imperfect conduction, cannot be altered by changing the strength of the stimulus which sets it up, but that in a series of impulses the intensity of all but the first will depend on the state of recovery of the nerve and will, therefore, vary with the interval separating each impulse from its predecessor.

Chapter III.—Summation and Inhibition of Impulses in Peripheral Nerve.

These facts make it easy to see how a form of summation may be produced in peripheral nerve by the correct timing of a series of impulses. There is, however, another type of summation which must be considered briefly because it is apt to be confused with the true summation of impulses. We have seen that an external stimulus brings about a local disturbance in the nerve-fibre which must reach a certain intensity before the impulse is set up at all. A stimulus just below the threshold strength will produce a disturbance which is not quite intense enough to start the impulse. However, this local disturbance will take a short time to subside, and if another stimulus of the same strength is applied before it has subsided the additional disturbance may be great enough to reach the intensity required to start the nervous impulse. Thus two inadequate stimuli applied at the same point within a very short time interval may set up a nervous impulse where one alone would fail. This form of summation is purely local; it does not occur if the two stimuli are sent in at different points on the nerve, as the excitatory disturbance is confined to the point at which the stimulus is applied. The effect [28], [24] is generally known as the summation of inadequate stimuli, or as the summation of local excitation, and it is an entirely different process to the summation of impulses with which we are concerned at present.

The summation of impulses implies that a single impulse may fail to be conducted successfully, whereas two or more will succeed, and it is therefore concerned with the conduction of the impulses and not with their initiation. It may be brought about in peripheral nerve in the following way. If a muscle-nerve preparation is arranged so that a narcotic can be applied over a length of nerve between the point of stimulation and the muscle, it is possible to adjust the degree of narcosis so that a single impulse just fails to pass through the affected area. Thus a single stimulus, however strong, will not lead to any contraction in the muscle. But if two stimuli are sent in so that the second occurs about 0·03 second after the first, the second impulse will be set up during the phase of increased activity and its intensity will be greater than the normal. It will be able to withstand a greater decrement than the first impulse and therefore it will pass through the narcotized region and lead to a contraction. Further stimuli occurring at the right intervals may set up a train of impulses of which each occurs in the phase of heightened activity left by its predecessor, and in this way each succeeding impulse may be able to pass the region in which the first was extinguished [9]. It would be possible to extend this explanation to cover cases in which the contraction does not occur until several impulses have been set up and have failed to reach the muscle. Each impulse might travel a little farther through the region of decrement than its predecessor and each would facilitate the conduction of the impulse following it, so that in the end an impulse would succeed in passing through without extinction. However, in this case we are treading on uncertain ground as the conditions have not yet been reproduced in isolated nerve.

A form of inhibition may be produced experimentally by much the same mechanism. Suppose that the degree of decrement is not quite enough to extinguish a single impulse, and that impulses are sent in at intervals of more than 0·015 second. Each of these impulses will be of normal or supernormal intensity and therefore all of them will reach the muscle and a sustained tetanus will be produced. If the frequency of the impulses is increased to 0·007 second, either by stimulating more rapidly at the same point or by stimulating at another point as well, the impulses will follow one another so rapidly that each will occur during the period of depressed activity following the passage of its predecessor. Thus each impulse will have an intensity less than normal and will be unable to pass through the region of decrement; the muscle will relax because no impulses can reach it, and its con-

traction will remain inhibited until the frequency of stimulation is reduced again to its original value. This type of inhibition was first described by Wedensky [48], though its mechanism was not clearly understood until Lucas [30] had analysed it more thoroughly.

It is possible to produce the same kind of inhibition by increasing the strength of the stimuli without altering their frequency. In this case we must start with stimuli occurring at an interval as small as 0·007 second and of a strength only just greater than the threshold. The first stimulus will set up an impulse, but the second will occur during the period of depressed excitability and it will not be strong enough to set up a second impulse. The nerve will have recovered completely by the time the third stimulus reaches it, and this will set up an impulse of normal intensity. The fourth stimulus will fail as the second failed, but the fifth will succeed again and so on. Thus the number of impulses set up will be only half the number of stimuli in a given time, and the interval between succeeding impulses will be great enough to allow complete recovery to take place between each. However, a strong stimulus is able to set up an impulse during the period of depressed excitability, and so if the strength of the stimuli is increased every one of them will be able to set up an impulse instead of every other one. For this reason an increase in the strength of the stimuli will double the frequency with which impulses are sent down the nerve, and, as before, the intensity of each impulse will be reduced and the muscle will cease to contract. In this case increasing the strength of the stimuli is simply equivalent to increasing the frequency of effective stimulation and the mechanism of inhibition is unchanged [31], [2].

The foregoing account of peripheral inhibition and summation is somewhat at variance with that given by Verworn and Fröhlich, but their theory has already been discussed at some length by Lucas [35] and shown to be in conflict with the experimental evidence. In the particular case of the frog's sciatic there can be little doubt that the foregoing explanation is correct, and it is also correct for the nerve to the crayfish's claw. It has not yet been fully demonstrated in a mammalian preparation because the experimental difficulties are greater, but there is ample evidence to show that the course of recovery proceeds along the same lines and there is no reason to suppose that any new factors come into play.

The whole mechanism of peripheral summation and inhibition may be summed up in a very few words. If there is an obstacle to con-

duction in the course of the nerve-fibre this obstacle may be surmounted by timing a series of impulses, so that all but the first are greater than the normal, and it may become insuperable if the impulses are timed so that all but the first are smaller than the normal. In the former case each impulse must be set up during the phase of heightened activity left by its predecessor and in the latter case each impulse must be set up during the phase of depressed activity.

Before these results can be considered as anything more than a purely artificial effect we have to consider how far the experimental "region of decrement" produced by narcotics is at all comparable with any of the regions of imperfect conduction occurring naturally in the course of the intact nervous system.

Chapter IV.—Nerve-endings and Synapses as Regions of Decrement.

It is clear that conduction across the nerve-ending in a muscle-nerve preparation and across the synapse in the central nervous system differs in several respects from conduction in a simple nerve-fibre. It is much more easy to investigate the nerve-ending and therefore we will begin with this. Now in the first place it is evident that the nerve-ending, taken in its widest sense as implying the whole of the junctional area between typical nerve-fibre and typical muscle-fibre, is not simply a region of decrement and nothing more. It is a region where conduction proceeds in one direction only, where the local excitatory mechanism reacts to much briefer currents than usual, and where certain drugs have a peculiar effect. None of these features can be reproduced by establishing a region of decrement in a nerve-trunk. But there is fairly good evidence that the nerve-ending is often a region of decrement as well. When the preparation is perfectly fresh the nerve-ending may be able to transmit an impulse set up in the early stages of recovery and therefore of very small intensity, but a relatively slight change in the perfusing fluid, such as an addition of $H^{\cdot}$ ions or absence of oxygen, will first of all increase the interval which must separate the two impulses, if the second is to reach the muscle, and will lead eventually to the failure of the first impulse also. A certain amount of confusion is introduced by the fact that we do not know how the rate of recovery of the nerve-ending is modified by these changes. Indeed the observation that in certain conditions the nerve-ending will no longer transmit a second impulse occurring very soon after the first

does not show that there is any decrement in conduction. It might be due entirely to a slowing of the rate of recovery of the nerve-ending, the impulse being extinguished not because it is of small intensity but because it reaches the nerve-ending at a time when this is still in the absolute refractory state. However, the ultimate result of these changes is to make the nerve-ending unable to conduct even an impulse of normal intensity, and at this stage there can be no doubt that conduction with a decrement comes into play. The condition is best realized by fatiguing the preparation by repeated stimulation [7]. By this method it is easy to reach a stage in which a single impulse is unable to reach the muscle at all, whereas a series of impulses separated by about 0·03 second will produce a tetanic contraction. As we have seen, an impulse occurring 0·03 second after its predecessor will have an intensity greater than the normal because it occurs in the phase of increased activity. Thus the nerve-ending may be brought into a state in which it will refuse to conduct an impulse of normal intensity but will conduct one of intensity greater than normal; in other words, it will conduct with a decrement which is just great enough to extinguish an impulse of normal intensity.

In certain preparations, e.g., the crayfish's claw, this condition may develop spontaneously and remain unchanged for long periods [33]; in the frog's sciatic-gastrocnemius preparation it is only produced after repeated stimulation and it passes off very quickly, but it seems more than likely that it is always present in a certain percentage of the nerve-endings, even in a perfectly fresh preparation. Thus it is found that the electric response of the muscle in answer to the second of two stimuli in the nerve is considerably larger than the first response when the interval between the stimuli is about 0·03 second [39], [8]. The effect does not occur when the stimuli are applied directly to the muscle fibres and it is presumably due to the fact that a greater number of muscle fibres are thrown into action by the second stimulus because the impulses which it sets up are large enough to pass nerve-endings which will not transmit an impulse of the normal intensity. This effect is found in the sartorius as well as in the gastrocnemius, and it appears to be present even when the preparation, judged by other standards, is in a perfectly normal state. We have, therefore, a type of summation occurring at the nerve-ending and depending on exactly the same mechanism as the summation which occurs at a region of decrement artifically established in the course of a nerve-fibre. Indeed it seems probable that in life some of the fibres of each muscle can only be called into play by a summation of impulses at the nerve-ending [19].

Inhibition can be produced at the nerve-ending instead of summation by timing a series of impulses so that each is of smaller intensity than the normal [30]. In this case the preparation must be moderately fatigued, so that the decrement at the nerve-ending is not quite large enough to extinguish a normal impulse. It is then found that a series of impulses occurring at shorter intervals than 0·01 second will produce an initial twitch, corresponding to the first impulse, followed by complete relaxation, whereas a series with a frequency of 0·02 or 0·03 second will give a sustained tetanus. Here also the nerve-ending behaves exactly like a region of decrement produced experimentally in the course of a nerve.

We are treading on much less certain ground when we compare the synapse in the central nervous system with the nerve-ending and with an experimental region of decrement. The evidence is very scanty, but it is at least agreed that the chief differences between conduction in the central nervous system and conduction in a peripheral nerve are due to the peculiar properties of the synapse, or junctional region between one neurone and another. It is argued that the actual cell body and nucleus are probably concerned only with the nutrition of the fibres, since the conduction of the posterior root fibres is unaffected by the presence of the ganglion cells on them, and in certain invertebrates Bethe [14] has been able to destroy the whole of the nerve-cells completely without interfering with the reactions of the central nervous system. The fibres themselves probably conduct in much the same way inside the central nervous system as outside it, and so by a process of exclusion we can locate the characteristic reactions of the central nervous system at the synapse.

These conclusions need a good deal of qualification. It is often assumed that there must be some definite synaptic membrane separating one neurone from another, and to question this would be to stir up the smouldering ashes of the neurone controversy. But we have certainly no evidence that the properties ascribed to the synapse are confined to the exact point where one neurone leaves off and another begins, although the analogy with the nerve-ending lends a certain amount of support to this view. As a matter of fact, there is a large junctional area where the nerve-fibres are modified by splitting up into dendrites, network formation, &c., and the reactions attributed to the synapse may be due to the whole or to any part of this area. Indeed, the reactions of the synapse might be produced by any part of the neurone other than the axons which are histologically identical

with peripheral nerve-fibres. However, it is clear enough that there are junctional regions in the central nervous system which behave very much like the nerve-ending, and whatever these regions may be histologically it is convenient to speak of them as synapses. They are susceptible to fatigue, to drugs and to lack of oxygen, they allow conduction in one direction only, they are often impassable to single impulses, and they admit of the summation and inhibition of a series of impulses. Whether this summation and inhibition is of the same nature as that produced at a nerve-ending or a region of decrement in simple nerve-fibre is a point which must be reserved for discussion until the next section, but although we have no rigid proof that the synapses are regions of decrement exactly comparable to those produced artificially, yet they are certainly regions of imperfect conduction, i.e., regions which only admit of the passage of an impulse under certain favourable conditions. Indeed, the whole working of the central nervous system depends upon this power of refusing certain impulses and allowing others to pass, and as the only form of imperfect conduction with which we are acquainted is that which occurs in a region of decrement, it is at least worth while to assume that the synapses are regions of decrement, and to see how this assumption tallies with the actual observations of conduction in the reflex arc.

There is at least one property in synaptic conduction which is absent in normal conditions both in peripheral nerve and in the nerve-ending as well. This is the property which enables a single impulse in the afferent nerve to set up a series of impulses in the efferent, so that the response may outlast the stimulus by several seconds. Veszi [47] has photographed the electric responses in the motor nerve of a frog under the influence of strychnine, and in this case a single stimulus applied to the posterior roots may set up ten or more impulses in the efferent nerve. This multiple response is an important factor in central conduction, but it does not necessarily imply any properties which are peculiar to the synapse, for a change in the ions of the perfusing fluid may easily bring a muscle or nerve into a condition in which a single stimulus will set up a large number of impulses. It is tempting to suppose that the effect depends on the increase of excitability which occurs in the third stage of recovery. If the initial excitability is very great this increase might be great enough to start a second impulse without any external stimulus. For instance, in the heart muscle the excitability rises to infinity after each refractory period is over and the tissue responds automatically; between this case

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and that of the motor nerve the difference appears to be one of degree only. However, it must be admitted that the rhythmic contractions of the frog's sartorius in a solution of NaCl may occur at intervals which are certainly too long to fit in with this hypothesis unless we assume that the time relations of the recovery process are considerably longer than usual [36]. Judging from Veszi's records the multiple responses in a reflex occur at intervals which would agree more or less with the periods of increased activity following each response. However, the precise mechanism of the effect is still very doubtful. Whatever this may be, the effect certainly exists and must be reckoned with in analysing the reactions of the reflex arc.

There is yet another point in which the reaction of the synapse differs from that of the nerve-trunk and that is in its great susceptibility to fatigue. The immense importance of fatigue in the economy of the central nervous system has been pointed out by Sherrington. As a rule a reflex path ceases to conduct at all after a short period of activity, whereas a peripheral nerve in the normal state will conduct without the least decrement after several hours' stimulation. The nerve-ending in muscle occupies an intermediate position, for the passage of a rapid succession of impulses through it increases the decrement in conduction and eventually leads to a complete block. The same fatigue effect is often met with in a nerve-fibre which has been narcotized so that it conducts with a decrement. By adjusting the strength of the narcotizing solution it is sometimes possible to arrive at a steady state short of complete failure of conduction, and in this state the decrement increases after the passage of a succession of impulses and returns slowly to its former value after stimulation has ceased. This fatigue is clearly of quite a different order to the momentary depression of function which constitutes the refractory state, and it is by no means certain that the refractory period is altered in any way when fatigue sets in. It is possible that the sole effect of fatigue is to increase any existing difficulty of conduction, though there may be a general depression of function as well. In any case when conduction occurs with a decrement, either in peripheral nerve or in the nerve-ending, the passage of a rapid succession of impulses does cause a temporary increase in the decrement, and presumably the same process may occur in the junctional regions of the central nervous system.

Chapter V.—Conduction in the Reflex Arc.

Taking all these differences into account we may construct the following model of the central nervous system. We may suppose it to consist of a number of neurones communicating with one another by junctional areas or synapses. The synaptic areas are regions of imperfect conduction; the impulse suffers a decrement as it passes through them, and this decrement is by no means constant, but varies, *inter alia*, with the amount of previous activity to which the neurone has been subjected. The duration of the refractory period and the extent of the change which occurs in the period of enhanced activity may vary in the same way and may have different values in different synapses or different parts of the same synapse. At some point in the synaptic region the passage of a single impulse may initiate a succession of impulses, and at some point conduction is possible in one direction only. The impulses which pass through the central nervous system are of the same nature as those set up in a simple nerve-fibre by an electric stimulus and they behave in the same way in regard to changes in intensity, passage through regions of imperfect conduction, &c.

This suggested scheme for the mechanism of the central nervous system has the advantage that it does not postulate any properties in central conduction which are not met with in a rudimentary state in conduction through simple tissues such as nerve or muscle fibre, and for this reason it should be possible to test it experimentally. It is true that there is very little direct experimental evidence at present, but we can see in a general way how the theory fits in with the observed facts of central conduction and where the chief difficulties are likely to arise.

In the first place we have to consider how the reaction of the central nervous system can be adjusted to different strengths of external stimulus if it is true that the size of the impulse follows the all-or-none principle in each nerve-fibre. Naturally a certain amount of grading is possible whenever there are a number of sensory end-organs of graded excitability, for in this case a stronger stimulus will set up impulses in a greater number of nerve-fibres. In the sensory organs of the skin it seems quite probable that the response of a single end-organ is of invariable intensity, for there is very little variation, if any, in the intensity of the sensation evoked by stimulating a single heat, cold, or touch spot. However, in the eye and the ear it is difficult to imagine that there are enough fibres to account for all the different intensities of sensation which can be perceived. The difficulty is not very serious, for the all-or-none principle is concerned with the relation between a

single stimulus and a single impulse. If the stimulus sets up a train of impulses it is quite possible that their frequency, and therefore their intensity, might vary with the strength of stimulation. We have no direct proof that in the end organs of the eye and ear a momentary stimulus does give rise to a series of impulses, but there is evidence that a strong electric stimulus applied to a peripheral nerve-trunk may sometimes give rise to several impulses instead of one only, so that the suggestion has some experimental support. In any case it is clear that the effect on the central nervous system of a series of impulses will depend on the frequency with which the impulses recur, and as this frequency is variable there is no reason to assume that the excitation of a single end-organ must always have the same result, however the organ is stimulated.

From another point of view the all-or-none principle simplifies matters considerably. Whatever our conception of the central nervous system may be, there can be little doubt that the amount of energy leaving it by the efferent nerves may be considerably greater than the amount entering it as the result of an external stimulus. A light touch which cannot set up impulses in more than a few sensory nerve fibres may lead to the forcible contraction of a number of muscles, and in this case the number of motor nerve-fibres in action must be very much greater than the number of sensory fibres. It is scarcely conceivable that the loss of energy involved in the passage of impulses down the motor nerves should not be very much greater than the gain which results from the passage of a few impulses into the central nervous system. Evidently there must be some form of relay in the reflex arc to account for this multiplication of impulses. It would be possible to account for this by supposing that each neurone, or each nerve cell, may act as a relay, sending out impulses of full intensity whatever the intensity of the impulses reaching it from the afferent side. However, the all-or-none principle shows that this assumption is unnecessary, for any part of a simple nerve fibre may act in this way. We have seen that an impulse may be reduced almost to vanishing point by passage through a region of decrement, but that as soon as it re-enters the normal fibre again it regains its full intensity. This recovery could only take place if the energy involved in the passage of the impulse is supplied locally from each point in the fibre through which the impulse passes, just as the explosion wave in a train of gunpowder is maintained by the energy in each part of the gunpowder as the wave reaches it and sets it alight. Consequently there is no reason to suppose that there

are definite relay stations in the central nervous system. Wherever an impulse passes down normal nerve-fibre its intensity will be the same whatever its former history may have been, and if an afferent fibre branches there is no reason to suppose that the impulses in each branch will be any smaller than the impulses in the original fibre in spite of the increased discharge of energy which will be necessary to maintain several impulses instead of one only. In the same way there is no reason to suppose that the impulse will become progressively smaller and smaller as it passes through successive junctional areas. It may be reduced in intensity in each area, but if it succeeds in passing through it will regain the normal intensity as soon as it leaves the region of decrement. Thus the relay effect of the central nervous system is simply due to the fact that it is a region where the afferent fibres branch repeatedly. Wherever this occurs there is the possibility of turning one impulse into two, and the increased energy required is supplied locally by the fibres themselves, just as it is supplied in peripheral nerve when an impulse regains its full intensity after reduction in a region of decrement.

If the central nervous system contains regions of decrement there should be no difficulty in accounting for at least one form of inhibition and summation. The presence of a region of decrement in peripheral nerve is the only condition necessary for the production of peripheral inhibition and summation and these effects depend simply on the normal course of recovery, according to which an impulse set up in the earlier stages of recovery has an intensity less than normal and an impulse set up in the later stages has an intensity greater than normal. If we consider the complications which are introduced in the central nervous system where the impulses have to pass through several relays of conductors and junctional regions with different rates of recovery, &c., it will be clear that the most varied possibilities are opened up without introducing any assumptions which have not been proved in the case of peripheral conduction.

The hypothesis is supported by various observations which show that the nature of the response in the reflex arc depends on the strength and frequency of the stimuli and also on the degree of decrement, just as it does in simple tissue. In the nerve-muscle preparation the inhibitory effect is produced by the extinction of impulses which follow so closely that they are all of subnormal intensity; thus the failure to reach the muscle will depend on the frequency of the impulses, the rate of recovery of the tissue and the degree of decrement which each

impulse must sustain on its journey to the muscle. An increase in the strength of the stimuli may also lead to inhibition because it will increase the frequency of the impulses set up. Now in the case of reflex inhibition there are several instances in which an increase in the strength or frequency of stimulation converts an excitatory stimulus into an inhibitory. Sherrington and Sowton [41] found that stimulation of the popliteal by weak currents caused a contraction in the extensors, whereas strong currents gave inhibition. Tiedermann [45] investigated the effects of varying frequency of stimulation in the frog under the influence of strychnine. In this case an increase in the rate of stimulation changes the end-effect from excitation to inhibition, and there is a further likeness to peripheral inhibition in that a series of rapidly repeated stimuli sometimes produces an initial twitch followed by inhibition, just as it does in a fatigued muscle-nerve preparation. Again Tiedermann and Veszi [45], [46] have shown that inhibition may be produced by simultaneous stimulation of two roots in the cord when the stimulation of either root alone will give a contraction. Here also the effect would seem to depend on the increased frequency of the impulses which reach the final common path when both roots are stimulated at once. A reversal of the reflex effect is also produced by the action of certain drugs. Bayliss [11] has shown that stimulation which normally leads to a vaso-constrictor reflex gives vaso-dilatation instead after chloroform has been administered. Sherrington and Sowton [42] found the same reversal in a limb reflex. The most important action of chloroform in a nerve-trunk is to produce a decrement in conduction and therefore it is only to be expected that in the central nervous system it should increase the already existing decrements and so lead to the extinction of impulses which were formally just large enough to reach the motor neurone.

If we grant that the synaptic regions may have different rates of recovery there is no difficulty in explaining the fact that stimulation of an afferent nerve may lead to contraction of one muscle and inhibition of its antagonist. We must suppose that the frequency of the impulses reaching the final common path of the inhibited muscle is so great that all the impulses are of subnormal intensity and are therefore extinguished before they reach the muscle. The frequency of the impulses reaching the muscle which contracts must be slower, so that the impulses shall be large enough to pass. These conditions will be realized if at some point on the path leading to the muscle which contracts there is a region which recovers so slowly that every other impulse from the

afferent nerve arrives during the absolute refractory period and is extinguished completely. The effect of this will be to halve the number of impulses passing towards the muscle, so that each will be large enough to avoid extinction; in the other path, where the impulses do not pass through a region of slow recovery, the frequency will be great enough to cause inhibition.

Most of the phenomena of reciprocal innervation may be accounted for by a mechanism of this type. However, difficulties begin to arise when we come to consider the balanced effects of inhibitory and excitatory stimuli. Sherrington [40] has shown in the case of voluntary muscle, and Bayliss [12] in the vaso-motor reflexes, that if an excitatory and an inhibitory nerve are excited at the same time the effect produced is a simple algebraic summation of the two single effects and depends entirely on the relative strengths of the two stimuli. Now, the frequency of the impulses in the central paths should be, if anything, greater when both nerves are stimulated than when the inhibitory nerve is acting by itself, and therefore the impulses should be still further reduced in intensity. Indeed, the stimulation of several afferent nerves in connection with the final common path should always result in inhibition, whatever their effects might be when acting alone. Veszi and Tiedermann have shown that this does occur in the spinal frog under the influence of strychnine, but Sherrington's records prove that the result is by no means constant. A strong stimulation of an excitatory nerve may break through a simultaneous inhibition and cause a contraction, and in certain cases rhythmic contractions are set up by stimulating an excitatory and an inhibitory nerve at the same time. To explain these effects we should have to introduce various subsidiary hypotheses as to the excitability of different nerve-fibres, the changes introduced by fatigue, &c., and though the suggested scheme is sufficiently elastic to admit of elaboration along these lines, it would be a mistake to insist on this until the evidence is much more complete. For the present we must be content to point out that the difficulty exists.

One of the most important features of the scheme suggested to account for reflex conduction is that the neurones are supposed to behave like peripheral nerve-fibres in regard to the impulses passing through them. We have assumed that the activity of the neurone cannot be continuous, but that each impulse must be followed by a short period of inactivity which passes off gradually in the various stages of recovery. As Forbes and Gregg have shown, when the

motor nerve is excited reflexly the impulses which pass down it are indistinguishable from those set up by direct stimulation, and we have no direct proof that any other form of activity is possible either in the nerve-fibre or in the neurones of the central nervous system. However, the reflexes which have been investigated from this point of view have all been of the type resulting in rapid contractions of the muscle and we know very little of the tonic postural reflexes. Buytendick [16] has shown that the electric response of a muscle in decerebrate rigidity has the usual oscillating character, but, as we have seen, there is a certain amount of evidence in support of the view that the tone of a muscle is controlled by a mechanism entirely different from that which regulates its rapid phasic contractions. The evidence is too complicated and, as yet, too inconclusive to be discussed in detail, but it shows that we must face the possibility that there may be some way of producing a continuous activity in certain neurones and certain parts of the muscle, an activity quite unlike the intermittent discharges which form the usual type of nervous impulse. If this is so, the production and inhibition of tone cannot be explained by the mechanism we have suggested, but all inhibition is not necessarily of the same nature and there is no reason to suppose that the inhibition which cuts short an active contraction is not identical with that produced experimentally in a region of decrement or nerve-ending. In this case the contraction is certainly maintained by a series of impulses in the motor nerve and its inhibition is due to the extinction of these impulses. Indeed, it is rather difficult to imagine that the tonic contraction in voluntary muscle is not produced and inhibited by the same mechanism, for when a contracting muscle is inhibited it relaxes completely and it seems an unnecessary complication to suppose that the relaxation is produced by two distinct mechanisms, one cutting short the phasic contraction and the other the residue of tone.

It would be idle to continue these speculations, for they have already gone far beyond the existing experimental basis. The suggested mechanism of central conduction may well prove to be completely absent or present only in a small degree in the central nervous system. However, the hypothesis has the advantage that it does not demand any properties in central conduction which cannot be shown to exist in some degree in simple conducting tissues, and as all these properties can be analysed without much difficulty in simple tissues it should be a fairly straightforward task to determine how far they will account for central conduction. The hypothesis may have been set up only to be

knocked down in the near future, but it is at least tangible enough to knock down and the process cannot fail to reveal something of the mechanism of the central nervous system.

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STIMULATION OF THE MOTOR CORTEX IN A MONKEY SUBJECT TO EPILEPTIFORM SEIZURES.

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In the higher mammals epileptiform convulsions can, as Magnan showed, be evoked by injection of absinthe; that strong faradization of the motor cortex may in the dog and monkey evoke an access of spasm of epileptoid character is a well-known laboratory experience. Stimulation of the cortex in an animal suffering from idiopathic epilepsy is, however, a laboratory experience of rarer occurrence; I have not succeeded in finding an instance of it recorded. The following observation may therefore appear worth mention here.

A "Jew" monkey (*Macacus fuliginosus*) received into the laboratory this spring was found to be subject to epileptoid attacks. These attacks had a characteristic form. The opening movement visible was retraction of the left angle of the mouth, whence contraction spread to all the facial muscles of that side and to the eyes. Then followed spasm of the neck, and of the left arm, and then of the left leg. The animal fell over to the left side. Finally, the right side became involved, though not so violently as the left. The attack lasted usually about two minutes, the animal lying seemingly unconscious, though with blinking eyes. The tongue was not bitten, nor was urine or fæces passed. When the convulsions had subsided the animal lay panting and would gaze about helplessly as though wondering what had happened. For a short period after each attack the limbs appeared to be paretic.

One cannot tell how often the animal was taken by these seizures; six seizures were, however, observed in the course of one week. In every observed instance the attack seemed to be induced by the taking into the mouth of a large morsel of food; indeed, it was found that the attack could be in some measure expected after giving the animal a too bulky slice of apple. The animal appeared in quite good health except for the epilepsy; it was an adult male.

After the animal had been under observation for some weeks, the motor cortex of both hemispheres was exposed under full chloroform narcosis. The cranial vault was found to be abnormally thick; where trephined in the upper parietal region the bone thickness measured 6 mm., which is about twice the usual measurement. The exposed cortex was tested by faradism with the unipolar method.

Abnormality of reaction was discovered nowhere except in the "tongue" area of the right hemisphere clearly, and less clearly in the "tongue" area of the left hemisphere. The threshold value of stimulus of the "tongue" area did not seem unusually low, or lower than that of such areas as "thumb or index finger," but each stimulation of the area unless extremely brief, e.g., less than 1 sec. and sometimes even then, provoked a tongue movement which almost immediately became clonic and epileptoid, meaning by the latter that it continued as a series of discharges after the faradic stimulus of the cortex had been withdrawn, and although it usually did not spread, it required a considerable period, e.g., a minute, for its subsidence. If the stimulus were continued for a few seconds the epileptoid movement did spread from the tongue to the muscles of the left angle of the mouth; occasionally it would involve all the facial muscles of the left side. By no persistence of the faradization could, however, the epileptoid movement be made to extend beyond the face. It never, unlike the natural seizures observed in the animal, spread to the neck or limbs even of the same side, let alone of the opposite.

The cortical area for retraction of angle of mouth itself did not seem to give abnormal responses; the area where opening of the jaw could be obtained seemed somewhat more extensive than usual, but otherwise normal. In the left hemisphere the tongue area yielded "epilepsy" discharges easily, though not so readily as did the tongue area of the right cortex, nor did the epileptiform discharge spread. Elsewhere throughout the motor region the reactions appeared entirely normal.

No gross indications of an anatomical kind were visible suggestive of abnormality in the cortex of either hemisphere.

In evaluating the experimental results it is to be remembered that limited epileptiform discharge is in the monkey's cortex usually obtainable by prolonged or quickly repeated faradic stimulations of almost any point in the motor cortex. The result observed with the tongue area of this animal was therefore a quantitative rather than a qualitative one. On the other hand, the exceptional readiness with which tongue "epilepsy" could be evoked is remarkable because, at least in my experience, the tongue area is not one from which epilepsy is usually easily provocable. Comparing the experimental result with the seizures observed in the animal clinically, it had not been noted for the latter that they began in the tongue. They may have done so and that point have escaped observation owing to the tongue lying hidden in the mouth.

INTRACRANIAL ANEURYSMS.

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My colleague, Dr. Fearnsides [1] in an article upon "Intracranial Aneurysms," published recently in this Journal, has honoured me by references to my paper [2] on "Alterations in Arterial Structure, and their Relation to Syphilis." Dr. Fearnsides, on pages 236 to 238, has attempted, by analysis of the statistics scattered throughout my paper, to show the relative frequency with which aneurysms within the cranium and within the body had been found in the Pathological Institute of the London Hospital. The result has demonstrated to me many defects in my writing. In the hope of removing these defects, as far as possible, I have obtained permission from Dr. Fearnsides to revise the analysis.

A comparative analysis of all the lesions tabulated in my paper was rendered impossible by my having in places analysed the records for 1908 to 1913, inclusive, and in places the records for 1907 to 1913, and by my having omitted the total number of examinations in the years 1908 to 1913. In order to draw up a comparative table it is necessary either to add to some of my statistics missing numbers for 1907, for instance twenty-six cases of syphilitic aortitis, or to deduct from others the numbers belonging to 1907. The latter form of correction gives the most accurate figures, because during the year 1907 our methods of controlling examinations and records were in process of evolution. When this correction is chosen, it is obvious that the total number of examinations during the years 1908 to 1913 must be supplied. Both Dr. Fearnsides and I have adopted as a definition of true aneurysm all dilatations of the whole arterial wall. I shall, therefore, first draw up a table, on similar lines to that of Dr. Fearnsides, so as to include all aneurysms which fell within this definition. I shall then, however, discuss the disadvantages attendant upon a comparative table in which this definition is employed, and the criticisms which I have received in respect of this definition. Finally, I shall attempt to remove these disadvantages, and meet these criticisms, by a second table based upon a modified definition of "aneurysm."

During the years 1908 to 1913, inclusive, in a total of 6,829 necropsies, there were 6,751 examinations of the body, and 4,547 examinations of the head; in 78 of these examinations of the head, examination of the body was not permitted.

TABLE I.

True Aneurysms of Aorta :—	
Due to syphilitic inflammation	175 cases
,, tuberculous inflammation, 1 example in	1 case
,, non-granulomatous inflammations, 4 examples in	4 cases
,, medial degeneration (focal, 18 cases ; diffuse, 4 cases +) ..	22 + cases
	202 + cases
Extensive Dissecting Aneurysms of Aorta :—	
Due to medial degeneration	5 cases
,, developmental deficiency	2 ,,
	7 cases
True Aneurysms of Other Large Elastic Arteries :—	
Due to syphilitic inflammation, 42 examples (all in cases included in above 175 cases of syphilitic aortitis) in	29 cases
,, medial degeneration (diffuse aneurysm)	+ ,,
	29 + cases
True Aneurysms of Small Elastic Arteries :—	
Due to tuberculous inflammation, 10 examples (all aneurysms in pulmonary vomicæ ; many such aneurysms had doubtless escaped detection) in	10 cases
True Aneurysms of Muscular Arteries (excluding the Cerebral Arteries) :—	
Due to syphilitic inflammation, 6 examples (all in cases included in above 175 cases of syphilitic aortitis) in	5 cases
,, infective embolism, 16 examples in	14 ,,
,, spread of non-granulomatous inflammation from without, 3 examples in	3 ,,
,, medial degeneration (focal, saccular, 12 examples in 7 cases ; focal associated with atheroma + ; diffuse +)	7 ++ cases
	29 ++ cases
True Aneurysms of Cerebral Arteries :—	
Due to infective embolism, 15 examples in	13 cases
,, medial degeneration following congenital developmental deficiency, 33 examples in	29 ,,
,, ,, ,, (diffuse + ; focal associated with atheroma +)	++
	42 ++ cases

This revised list gives, I believe, a true comparative analysis of our records. It is, however, of no service for exact comparison, because I am unable to give under every specified cause either the exact number of examples of aneurysm or the exact number of cases in which aneurysms

occurred. To estimate the total number of aneurysms, as defined by Dr. Fearnsides and by me, would, for instance, in most cases of syphilitic aortitis, have been an almost impossible task owing to their great number. Still greater difficulty would have attended an attempt to ascertain and record the exact number of cases exhibiting certain forms of aneurysmal dilatation of which I merely mentioned in my paper the frequent occurrence. Thus, in regard to aneurysmal dilatation due to medial degeneration of the aorta, I recorded eighteen cases in which there were "small pitted or wrinkled areas," and four cases of "very marked, diffuse dilatation." In a preceding paragraph, however, I mentioned that diffuse dilatation of the aorta, especially of the thoracic aorta, was a very frequent sequence of medial degeneration and "is easily recognized in almost every male over the age of 50." I also stated that in the other large elastic arteries, "slight diffuse dilatation frequently results from medial degeneration." Again, in regard to aneurysmal dilatation of the muscular arteries due to medial degeneration, I recorded, in Table VII, seven cases in which there were saccular dilatations of muscular arteries other than the cerebral. I had, however, previously mentioned (pp. 244-5) that diffuse dilatation due to medial degeneration "is frequently found in the muscular arteries," including the cerebral arteries, and that "slight focal dilatation may be present at the sites of atheromatous plaques," this being "almost constant in atheroma of the cerebral arteries."

Even if I was in a position to make the above table complete by the substitution of exact numbers of cases for the sign +, the list would, as I have learned from correspondence, give a false impression to the majority of readers. This is the consequence of the definition of "true aneurysm" which has been adopted by Dr. Fearnsides and by me. I believe that our definition, which includes every dilatation of the whole wall, is both the only scientific and the only really practicable definition. This definition includes, however, a very large number of dilatations which the clinician, at any rate, would never regard as aneurysms. Indeed, one kindly critic wrote that he regretted my "old-fashioned" definition, and would have had me apply the term aneurysm to saccular dilatations alone. In a general discussion on the causation of aneurysm it would obviously be impossible to accept no dilatation as an aneurysm unless it was saccular. The small crateriform pits and narrow sulci, for instance, which are almost constant in syphilitic aortitis, are all potential saccular aneurysms. Areas which show, post mortem, only such minute dilatations may be more widely dilated during life; thus, the aortic commissure may post mortem only show small sulci in an intima con-

spicuously thickened by inflammation, and the aortic valves may be competent to the water test, although clinical observation and the post-mortem appearances of the heart prove that relative incompetence of the valves had been present during life. There are diffuse dilatations which all investigators would call aneurysms, and which give clinical signs and symptoms similar to those caused by saccular aneurysms. Further, I have found it impossible to estimate exactly what is to be regarded as a saccular dilatation. For exact definition of a saccular dilatation some arbitrary proportion between depth and diameter would require to be determined and universally accepted.

I realize, however, the desirability of attempting to distinguish between what might be called "practical" and "academic" aneurysms; I realized this when preparing my paper. Without such a distinction it would appear impossible to compare our figures with those of other observers. The aneurysms in the cerebral arteries tabulated as due to congenital weakness and to infective embolism, and certain aneurysms in the other muscular arteries due to medial degeneration, were unquestionably saccular and would be regarded by all as aneurysms. In the cases, however, of syphilitic inflammation of the aorta, other large elastic arteries and muscular arteries, and in the cases of medial degeneration of the aorta, I was unable to determine a satisfactory distinction between the practical and academic dilatations. I attempted to make a distinction by quoting the number of dilatations which had given rise to clinical manifestations by rupture, by pressure, or, in the case of aortitis, by causing relative incompetence of the aortic valves. A distinction based on such clinical criteria is, however, obviously imperfect. In a fresh attempt to make the distinction, I have made the following modification in our definition. I have only accepted as aneurysms: (1) definitely saccular dilatations; (2) saucer-like dilatations; and (3) sharply defined, focal, fusiform dilatations. For convenience I have referred to the shallow, saucer-like dilatations as "pouches." With this modified definition I have compiled Table II. This table includes, I think, all the dilatations which would have been accepted as aneurysms by all. In the case of syphilitic inflammation of the aorta and other large elastic arteries, and especially in the case of medial degeneration of the aorta, dilatations are also included which would probably not be considered, by the majority, worthy of the term aneurysm. Inasmuch, however, as Dr. Fearnsides compiled his table in order to show the exceptionally large number of cerebral aneurysms in the records of the London Hospital Pathological Institute, it is well that, if the modified definition

should err, it should err by including too many aneurysms of arteries other than the cerebral.

I regret that I am unable even with this modified definition to give the exact number of aneurysms in syphilitic aortitis; in several cases small examples have merely been recorded as "multiple."

TABLE II.

Focal, Saccular, Saucer-shaped and Fusiform Aneurysms, 1908-1913—Aorta :—			
Due to syphilitic inflammation (in 23 cases shallow pouches only)	Examples,	114	+ in 83 cases
,, tuberculous inflammation	,,	1	,, 1 ,,
,, non-granulomatous inflammation	,,	4	,, 4 ,,
,, medial degeneration (all very small or shallow pouches)	,,	4	,, 4 ,,
	Examples,	123	+ in 92 cases
Other Large Elastic Arteries :—			
Due to syphilitic inflammation (all cases are present also in the above 83 cases of syphilitic aneurysms of aorta)	Examples,	6	in 6 cases
Small Elastic Arteries :—			
Due to tuberculous inflammation (in vomicæ) ..	Examples,	10	in 10 cases
Muscular Arteries (excluding Cerebral Arteries) :—			
Due to syphilitic inflammation (1 case is present also in the above 83 cases of syphilitic aneurysms of aorta)	Examples,	2	in 2 cases
,, infective embolism	,,	16	,, 14 ,,
,, spread of non-granulomatous inflammation from without	,,	3	,, 3 ,,
,, medial degeneration	,,	12	,, 7 ,,
	Examples,	33	in 26 cases
Cerebral Arteries :—			
Due to infective embolism	Examples,	15	in 13 cases
,, medial degeneration following congenital developmental deficiency	,,	33	,, 29 ,,
	Examples,	48	in 42 cases

In regard to aneurysms caused by syphilitic inflammation of the large elastic arteries other than the aorta, and of the muscular arteries, it must be emphasized that in all the cases recorded in this table and in Table I the syphilitic inflammation involved vessels close to the aorta, and the aorta was affected by similar inflammation. Thus, of the syphilitic aneurysms of the large elastic arteries recorded in both tables the aneurysm farthest from the inflamed aorta lay in the upper two inches of the right common carotid, the lower inch of this artery also

showing evidence of inflammation to the naked eye; of the syphilitic aneurysms of the muscular arteries the aneurysm farthest from the inflamed aorta lay in the centre of the splenic artery. This aneurysm is one of the two recorded in Table II. It was associated with gummata in the peritoneal tissue round the pancreas, in addition to aortitis. In this case the infection had probably arisen independently of the aortitis. In all the remaining cases of syphilitic inflammation of the large elastic and muscular arteries in Table I and Table II the inflammation would appear to have been merely an extension from the aorta.

If Table II is accepted for purposes of comparison, then aneurysms of the aorta occurred in 92 cases or in 1·36 per cent. of examinations of the body. Aneurysms of large elastic arteries other than the aorta occurred in 6 cases; all these aneurysms were due to syphilitic inflammation and were accompanied by aneurysms of the aorta. Aneurysms of muscular arteries, other than the cerebral arteries, occurred in 26 cases, or 0·38 per cent. of examinations of the body; only 2 of these aneurysms were due to syphilitic inflammation; both of these were accompanied by syphilitic aortitis, 1 by an aneurysm of the aorta. Aneurysms of cerebral arteries occurred in 42 cases, or in 0·92 per cent. of examinations of the head; in 13 cases the aneurysms were caused by infective embolism, and 3 of these 13 cases are recorded also in the list of cases of embolic aneurysms in other muscular arteries.

If aneurysms in tuberculous vomicæ and in peptic erosions or ulcers are omitted, the following table compares the number of cases in which aneurysms were found in the arteries of the body with the number of cases in which aneurysms were found in the head, during the years 1908 to 1913:—

Cases with aneurysms of arteries in the body	..	117, *i.e.*, 1·73 per cent. of examinations.	
,, ,, ,, ,, *cranium*	..	42, ,, 0·92 ,, ,, ,,	

The cases which Dr. Fearnsides quotes, from the literature, of aneurysms of cerebral arteries caused by syphilitic inflammation, remind me of another, serious, omission from my original paper. I should have stated explicitly that I had attempted to give an account of personal observations on alterations in arterial structure, that I had given references to papers to which I was indebted for information, but that I had not examined the literature in order to ascertain to what extent my observations and conclusions corresponded to those of others. My observations were not confined to the cases given in my tables. At the time the paper was written I had seen over 9,000 necropsies in two

general hospitals. It was perhaps presumptuous to decide what conditions were rare on this material alone, although, on the other hand, rare cases are more likely than common to be recorded in the literature. In this connection I may add that a subsequent 1,500 necropsies have not given me an aneurysm due to syphilitic inflammation in a cerebral artery. Immediately after publication I regretted, for another reason, this omission of an explicit statement of the method in which my paper was written. I realized that in its absence I would appear to claim priority for conclusions which other workers had already published. I had, and have, no doubt that the great majority of my observations and conclusions, if correct, could be found in previous publications; there must be very many, besides those quoted by Dr. Fearnsides, whose work I had merely confirmed.

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